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PATENT ABSTRACTS OF JAPAN

(11)Publication number : **09-278718**
(43)Date of publication of application : **28.10.1997**

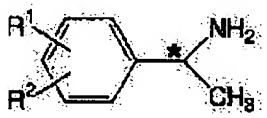
(51)Int.CI. **C07C211/27**
C07C209/88
C07C211/29
C07C213/10
C07C217/58
// C07B 57/00
C07M 7:00

(21)Application number : **08-084041**
(22)Date of filing : **05.04.1996**

(71)Applicant : **SUMITOMO CHEM CO LTD**
(72)Inventor : **HAGITANI KOJU**

(54) OPTICAL RESOLUTION OF 1-PHENYLETHYLAMINE COMPOUND

(57)Abstract:
PROBLEM TO BE SOLVED: To easily perform optical resolution of a 1-phenylethylamine compound in high yield without using particular apparatuses.
SOLUTION: A 1-phenylethylamine compound of the formula (R1 and R2 are each H, a halogen, an alkoxy, a haloalkyl or nitro; * represents asymmetric carbon; R1 and R2 are not Cl at the same time) is subjected to optical resolution with an optically active mandelic acid in a dialkyl ether of the formula R3-O-R4 (R3 is a 1-6C alkyl; R4 is a 4-6C alkyl).



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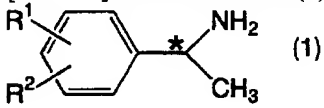
CLAIMS

[Claim(s)]
[Claim 1] General formula (1)



(1)

(R1 and R2 show a hydrogen atom, a halogen atom, an alkoxy group, a halo alkyl group, or a nitro group among a formula, respectively, and * shows an asymmetric carbon atom.) However, R1 R2 is not a chlorine atom simultaneously. An optical-activity mandelic acid is used for 1-phenyl ethylamines shown, and it is a general formula (2).
R3 -O-R4 (2
(-- R3 shows the alkyl group of carbon numbers 1-6 among a formula, and R4 shows the alkyl group of carbon numbers 4-6, respectively The optical-resolution technique of 1-phenyl ethylamines characterized by carrying out optical resolution in the dialkyl ether shown by).
[Claim 2] The optical-resolution technique of 1-phenyl ethylamines characterized by obtaining the diastereomeric salt of the optically active substance of 1-phenyl ethylamines, and an optical-activity mandelic acid, and subsequently carrying out the alkali treatment of this diastereomeric salt after melting 1-phenyl ethylamines and the optical-activity mandelic acid which are shown by the general formula (1) in the dialkyl ether shown by the general formula (2).
[Claim 3] The optical-resolution technique of 1-phenyl ethylamines according to claim 1 or 2 characterized by the dialkyl ether being a methyl-t-butyl ether.
[Claim 4] The optical-resolution technique of 1-phenyl ethylamines according to claim 1 or 2 that the amount of the dialkyl ether used is characterized by being 2 - 100 weight twice to 1-phenyl ethylamines.
[Claim 5] The optical-resolution technique of 1-phenyl ethylamines according to claim 1 or 2 that the amount of the optical-activity mandelic acid used is characterized by 0.1-1.2 mol being twice to 1-phenyl ethylamines.

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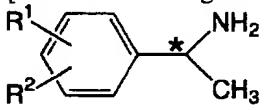
DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[The technical field to which invention belongs] this invention relates to the optical-resolution technique of 1-phenyl ethylamines.
[0002]
[Description of the Prior Art] The optically active substance of 1-phenyl ethylamines is a compound useful as intermediate fields, such as the physic and a pesticide. The technique of carrying out optical resolution of the racemic modification in a solvent, using an optical-activity mandelic acid as technique of obtaining the optically active substance of such 1-phenyl ethylamines etc. is common, after melting racemic modification and the optical-activity mandelic acid of 1-phenyl ethylamines in a solvent especially, the diastereomeric salt of the optically active substance of 1-phenyl ethylamines and an optical-activity mandelic acid is obtained, and the technique of subsequently carrying out the alkali treatment of this diastereomeric salt etc. is learned widely.
[0003] Although the technique using water (JP,56-26848,A), aqueous ammonia (JP,6-1757,A), and a methanol (Bull.Chem.Soc.Jpn., 66, 3414 (1993)) as a solvent at the time of obtaining diastereomeric salt conventionally etc. is proposed The technique using water is difficult for the filterability of the obtained diastereomeric salt to filter it bad. The technique using aqueous ammonia needed the special facility for dealing with aqueous ammonia, and since the technique using a methanol had little yield of the optical-activity 1-phenyl ethylamines made into the purpose, it was not able to be said that each of such technique was the technique which may fully be satisfied industrially.
[0004]
[Problem(s) to be Solved by the Invention] Then, this invention person resulted in this invention, as a result of inquiring zealously that the technique of carrying out optical resolution of the 1-phenyl ethylamines with easy and high yield should be developed, without using a special facility.
[0005]
[Means for Solving the Problem] That is, this invention is a general formula (1).



(1)

(R1 and R2 show a hydrogen atom, a halogen atom, an alkoxy group, a halo alkyl group, or a nitro group among a formula, respectively, and * shows an asymmetric carbon atom.) However, R1 R2 is not a chlorine atom simultaneously. An optical-activity mandelic acid is used for 1-phenyl ethylamines shown, and it is a general formula (2).
R3 -O-R4 (2
(-- R3 shows the alkyl group of carbon numbers 1-6 among a formula, and R4 shows the alkyl group of carbon numbers 4-6, respectively The optical-resolution technique of 1-phenyl ethylamines characterized by carrying out optical resolution in the dialkyl ether shown by) is offered.
[0006]
[Embodiments of the Invention] As a halogen atom [on 1-phenyl ethylamines applied to this invention, and in a substituent R1 and R2], a methoxy machine, the ethoxy base, etc. are illustrated as an alkoxy group, and a fluorine atom, a chlorine atom, a bromine atom, etc. are illustrated for a truffe ****** methyl group, difluoromethyl group, a ********** methyl group, etc. as a halo alkyl group, respectively.
[0007] As such 1-phenyl ethylamines For example, 1-phenyl ethylamine, 1-(2-fluoro phenyl) ethylamine, 1-(3-fluoro phenyl) ethylamine, 1-(2-chlorophenyl) ethylamine, 1-(3-chlorophenyl) ethylamine, 1-(2-****** phenyl) ethylamine, 1-(monochrome halo substitute phenyl) ethylamines, such as 1-(3-****** phenyl) ethylamine 1-(monochrome alkoxy substitute phenyl) ethylamines, such as 1-(2-methoxypheny) ethylamine and 1-(3-methoxypheny) ethylamine 1-(dialkoxy substitute phenyl) ethylamines, such as 1-(3, 4-dimethoxy phenyl) ethylamine 1-(2-truffe ****** methylphenyl) ethylamine, 1-(3-truffe ****** methylphenyl) ethylamine, 1-(nitroglycerine phenyl) ethylamines, such as 1-(halo alkylation phenyl) ethylamines, such as 1-(3-difluoro methylphenyl) ethylamine, 1-(2-nitroglycerine phenyl) ethylamine, and 1-(3-nitroglycerine phenyl) ethylamine, are mentioned. Each of these 1-phenyl ethylamines can be easily manufactured by the ********** (Leukert) reaction which uses acetophenones as a raw material [Organic Reaction Vol.5, pp.301-330 (1949)].
[0008] Although two kinds of optically active substance centering on the asymmetric carbon atom shown by * exists in 1-phenyl

ethylamines shown by such general formula (1), 1-phenyl ethylamines used for the technique of this invention may be those mixture, and it may be racemic modification.
[0009] an optical-activity mandelic acid -- any of D-mandelic acid and L-mandelic acid -- you may be -- the amount used -- 1-phenyl ethylamines -- receiving -- usually -- 0.1-1.2 mol twice -- it is a twice as many 0.3-1 mol domain as this preferably
[0010] substituent R3 in the dialkyl ether shown by the general formula (2) ****** -- the alkyl group of the carbon numbers 1-6, such as a methyl group, an ethyl group, and n-propyl group, -- substituent R4 ****** -- the alkyl group of the carbon numbers 4-6, such as n-butyl, t-butyl, and n-hexyl machine, is mentioned, respectively As such dialkyl ether, a methyl-t-butyl ether, an ethyl-t-butyl ether, a methyl-n-butyl ether, an ethyl-n-butyl ether, etc. are mentioned, for example, and a methyl-t-butyl ether (MTBE is called hereafter.) is used preferably especially. These dialkyl ether mixes independent or two sorts or more, respectively, is used, and may contain the organic solvent and water of further others. The amount of such dialkyl ether used is usually a twice [2 - 100 weight] as many domain as this to 1-phenyl ethylamines.
[0011] What is necessary is to obtain the diastereomeric salt of the optically active substance of 1-phenyl ethylamines, and an optical-activity mandelic acid, and just to carry out the alkali treatment of this diastereomeric salt subsequently, after melting 1-phenyl ethylamines and an optical-activity mandelic acid in the dialkyl ether in case of optical resolution, for example.
[0012] It faces melting 1-phenyl ethylamines and an optical-activity mandelic acid in the dialkyl ether, 1-phenyl ethylamines and an optical-activity mandelic acid may be added, for example to the dialkyl ether, both may be melted, the dialkyl ether solution of 1-phenyl ethylamines and the dialkyl ether solution of an optical-activity mandelic acid may be mixed, and the salt with 1-phenyl ethylamines and the optical-activity mandelic acid which both were made to react and obtained them further beforehand may be melted in the dialkyl ether. A melting temperature is usually a domain below the boiling point of 15 degrees C or more and the dialkyl ether.
[0013] Although one [of 1-phenyl ethylamines] optically active substance forms the diastereomeric salt with an optical-activity mandelic acid preferentially and this diastereomeric salt separates by usual technique, for example, the technique of cooling and condensing etc., you may make such diastereomeric salt separate by putting or stirring as it is by the case after lysis.
[0014] Although this is taken out after a precipitation of diastereomeric salt and it dissociates with a mother liquor, such diastereomeric salt is excellent in filterability, and can separate both easily by usual filtration operation etc.
[0015] The diastereomeric salt of the optically active substance of 1-phenyl ethylamines and the optical-activity mandelic acid which are obtained in this way is easily led to the optically active substance of 1-phenyl ethylamines by carrying out an alkali treatment.
[0016] In case of an alkali treatment, bases, such as a sodium hydroxide, a potassium hydroxide, a sodium carbonate, and a sodium hydrogencarbonate, are usually used, and the amount used is usually a twice as many 1-5 mol domain as this to diastereomeric salt. Such a base is usually used as aqueous solution, and the concentration is usually 5 - 20% of the weight of a domain preferably one to 50% of the weight.
[0017] The domain of processing temperature is usually -10-50 degrees C that what is necessary is just to mix the aqueous solution and diastereomeric salt of a base in case of an alkali treatment, for example.
[0018] Although the optically active substance of 1-phenyl ethylamines generates by such alkali treatment, this may be taken out by the technique of separating what carried out the layer separation in the reaction mixture after an alkali treatment by the case etc., and may be easily taken out from this reaction mixture by the technique of carrying out extraction processing, for example using an organic solvent insoluble in water, and carrying out solvent distilling off of the obtained organic layer etc. In the case of the latter, as an insoluble organic solvent, aromatic system solvents, such as ester system solvents, such as ether system solvents, such as the same dialkyl ether and the same diethylether, and a dioxane, and ethyl acetate, toluene, a xylene, and a chlorobenzene, etc. are used for water with having described above, for example, and the amount used is usually a twice [0.1 - 5 weight] as many domain as this to the diastereomeric salt used for the previous alkali treatment.
[0019] In addition, reaction mixture after taking out the optically active substance of 1-phenyl ethylamines contains an optical-activity mandelic acid, and such optical-activity mandelic acids can be easily collected from this reaction mixture, and it can carry out a reuse to the technique of this invention. Although it extracts in the same water using an insoluble organic solvent and the technique of carrying out solvent distilling off of the obtained organic layer etc. is mentioned to it with having described above after adding mineral acids, such as a hydrochloric acid, a sulfuric acid, and a phosphoric acid, for example to a water layer and making the pH into the domain of 0.5-2 as the recovery technique of such an optical-activity mandelic acid Since a reuse can be carried out to the technique of this invention, without distilling a solvent out of the obtained organic layer when the dialkyl ether is used as such an organic solvent, it is desirable.
[0020] Although the optically active substance of 1-phenyl ethylamines is obtained in this way, the optically active substance of another side which is an antipode with this is contained in the mother liquor after previous filtration operation separates diastereomeric salt, and after washing usual technique, for example, a mother liquor, from such a mother liquor using the alkaline aqueous solutions, such as the sodium-hydroxide aqueous solution, etc., it can be easily obtained by the technique of distilling off a solvent etc.
[0021]
[Effect of the Invention] According to the technique of this invention, optical resolution of the 1-phenyl ethylamines can be easily carried out with high yield, without using a special facility.
[0022]
[Example] Hereafter, this invention is not limited by these examples although an example explains this invention to a detail more. In addition, it asked for the optical purity of obtained 1-phenyl ethylamines by the high-speed liquid

chromatographic-analysis method for using an optical-activity column.

[0023] Example 1(RS)-1-phenyl-ethylamine 56g was melted in MTBE60g, it heated at 45 degrees C under stirring, and, in addition, the solution which, subsequently to MTBE180g, melted and obtained 31.7g of L-mandelic acids to this under stirring at this temperature was further stirred for 30 minutes at this temperature over 30 minutes. Then, cool to 20 degrees C over 6 hours, and the diastereomeric salt of a (S)-1-phenyl ethylamine and L-mandelic acid was made to separate, subsequently, by filtration operation, diastereomeric salt was obtained and the mother liquor was obtained simultaneously. After washing this diastereomeric salt twice using MTBE100g, it was made to dry, and 56.8g of diastereomeric salt was obtained. Subsequently, 185g of the sodium-hydroxide aqueous solutions was added 5%, the extraction using MTBE45g was performed twice after stirring for 30 minutes at 25 degrees C, after doubling an organic layer, the solvent was distilled off, and (S)-1-phenyl-ethylamine 25.2g (87%ee) was obtained.

[0024] After having doubled the washings after washing the mother liquor and diastereomeric salt which were obtained above and adding 18g of the sodium-hydroxide aqueous solutions 5%, extraction processing using MTBE30g was performed twice, after doubling an organic layer, the solvent was distilled off, and (R)-1-phenyl-ethylamine 30.8g (70.4%ee) was obtained.

[0025] Example 2(RS)-1-(2-fluoro phenyl) ethylamine 5g is melted in MTBE10g. The solution which melted and obtained 2.46g of L-mandelic acids to MTBE30g is dropped and added to this over 30 minutes, stirring under this temperature, after heating at 45 degrees C, the bottom of stirring of this, and. Furthermore, after stirring for 30 minutes, cool to 20 degrees C over 3 hours, and the diastereomeric salt of a (S)-1-(2-fluoro phenyl) ethylamine and L-mandelic acid was made to separate, subsequently, by filtration operation, diastereomeric salt was obtained and the mother liquor was obtained simultaneously. It dried, after washing this diastereomeric salt twice using MTBE10g, and 4.6g of diastereomeric salt was obtained. Subsequently, 16g of the sodium-hydroxide aqueous solutions was added 5%, the extraction using MTBE10g was performed twice after stirring for 30 minutes at 25 degrees C, after doubling an organic layer, the solvent was distilled off, and (S)-1-(2-fluoro phenyl) ethylamine 2.2g (87.2%ee) was obtained.

[0026] The washings after washing the mother liquor and diastereomeric salt which were obtained above was doubled, after washing 5% using 13g of the sodium-hydroxide aqueous solutions, the solvent was distilled off, and (R)-1-(2-fluoro phenyl) ethylamine 2.8g (71.6%ee) was obtained.

[0027] Example 3(RS)-1-(3-methoxypheny) ethylamine 5g is melted in MTBE20g. The solution which melted and obtained 2g of L-mandelic acids to MTBE20g is dropped and added to this over 30 minutes, stirring under this temperature, after heating at 50 degrees C, the bottom of stirring of this, and. Furthermore, after stirring for 30 minutes, cool to 20 degrees C over 3 hours, and the diastereomeric salt of a (S)-1-(3-methoxypheny) ethylamine and L-mandelic acid was made to separate, subsequently, by filtration operation, diastereomeric salt was obtained and the mother liquor was obtained simultaneously. It dried, after washing this diastereomeric salt twice using MTBE10g, and 4.1g of diastereomeric salt was obtained. Subsequently, 16g of the sodium-hydroxide aqueous solutions was added 5%, the extraction using MTBE10g was performed twice after stirring for 30 minutes at 25 degrees C, after doubling an organic layer, the solvent was distilled off, and (S)-1-(3-methoxypheny) ethylamine 2g (55.4%ee) was obtained.

[0028] After washing 5% using 13g of the sodium-hydroxide aqueous solutions together with a washings after washing the mother liquor and diastereomeric salt which were obtained above, the solvent was distilled off, and (R)-1-(3-methoxypheny) ethylamine 3g (43.8%ee) was obtained.

[0029] The solution which mixed and obtained example of comparison 1(RS)-1-(3-methoxypheny) ethylamine 5g, 2g [of L-mandelic acids], and methanol 13g was heated at 60 degrees C, and was stirred for 30 minutes under this temperature. When it became 30 degrees C, cooling to 20 degrees C over 3 hours, 0.01g of the diastereomeric salt of a (S)-1-(3-methoxypheny) ethylamine (99.9% of the optical-purity (S) fields, 0.1% of (R) fields) and L-mandelic acid was added as seed crystal. After cooling at 20 degrees C, by filtration operation, the diastereomeric salt of a (S)-1-(3-methoxypheny) ethylamine and L-mandelic acid was obtained, and the mother liquor was obtained simultaneously. It dried, after washing this diastereomeric salt once using methanol 3g, and 1.2g of diastereomeric salt was obtained. Subsequently, 10g of the sodium-hydroxide aqueous solutions was added 5%, the extraction using toluene 10g was performed twice after stirring for 30 minutes at 25 degrees C, after doubling an organic layer, the solvent was distilled off, and (S)-1-(3-methoxypheny) ethylamine 0.6g (88.2%ee) was obtained.

[0030] After having doubled the washings after washing the mother liquor and diastereomeric salt which were obtained above and adding toluene 10g, it washed 5% using 13g of the sodium-hydroxide aqueous solutions, the solvent was distilled off, and (R)-1-(3-methoxypheny) ethylamine 4.4g (12.2%ee) was obtained.

[0031] Example 4(RS)-1-(2-nitroglycerine phenyl) ethylamine 3.1g is melted in MTBE15g. The solution which melted and obtained 1.3g of L-mandelic acids to MTBE15g is dropped and added to this over 30 minutes, stirring under this temperature, after heating at 45 degrees C, the bottom of stirring of this, and. Furthermore, after stirring for 30 minutes, cool to 20 degrees C over 3 hours, and the diastereomeric salt of a (S)-1-(2-nitroglycerine phenyl) ethylamine and L-mandelic acid was made to separate, subsequently, by filtration operation, diastereomeric salt was obtained and the mother liquor was obtained simultaneously. It dried, after washing this diastereomeric salt twice using MTBE5g, and 2.4g of diastereomeric salt was obtained. Subsequently, 10g of the sodium-hydroxide aqueous solutions was added 5%, the extraction using MTBE10g was performed twice after stirring for 30 minutes at 25 degrees C, after doubling an organic layer, the solvent was distilled off, and (S)-1-(2-nitroglycerine phenyl) ethylamine 1.3g (90.4%ee) was obtained.

[0032] The washings after washing the mother liquor and diastereomeric salt which were obtained above was doubled, after washing 5% using 10g of the sodium-hydroxide aqueous solutions, the solvent was distilled off, and (R)-1-(2-nitroglycerine phenyl) ethylamine 1.8g (61.6%ee) was obtained.

[0033] Example 5(RS)-1-(3-truffe ****** methylphenyl) ethylamine 4g is melted in MTBE20g. The solution which melted and obtained 1.6g of L-mandelic acids to MTBE15g is dropped and added to this over 30 minutes, stirring under this temperature, after heating at 45 degrees C, the bottom of stirring of this, and. Furthermore, after stirring for 30 minutes, cool to 20 degrees C over 3 hours, and the diastereomeric salt of a (S)-1-(3-truffe ****** methylphenyl) ethylamine and L-mandelic acid was made to separate, subsequently, by filtration operation, diastereomeric salt was obtained and the mother liquor was obtained simultaneously. It dried, after washing this diastereomeric salt twice using MTBE5g, and 3.3g of diastereomeric salt was obtained. Subsequently, 10g of the sodium-hydroxide aqueous solutions was added 5%, the extraction using MTBE10g was performed twice after stirring for 30 minutes at 25 degrees C, after doubling an organic layer, the solvent was distilled off, and (S)-1-(3-truffe ****** methylphenyl) ethylamine 1.8g (60%ee) was obtained.

[0034] The washings after washing the mother liquor and diastereomeric salt which were obtained above was doubled, it washed 5% using 10g of the sodium-hydroxide aqueous solutions, the solvent was distilled off, and (R)-1-(3-truffe ****** methylphenyl) ethylamine 2.2g (50%ee) was obtained.

[0035] Example 6(RS)-1-(3, 4-dimethoxy phenyl) ethylamine 20g is melted in MTBE30g. The solution which melted and obtained 7.6g of L-mandelic acids to MTBE80g is dropped and added to this over 30 minutes, stirring under this temperature, after heating at 45 degrees C, the bottom of stirring of this, and. Furthermore, after stirring for 30 minutes, cool to 20 degrees C over 3 hours, and the diastereomeric salt of a (R)-1-(3, 4-dimethoxy phenyl) ethylamine and L-mandelic acid was made to separate, subsequently, by filtration operation, diastereomeric salt was obtained and the mother liquor was obtained simultaneously. It dried, after washing this diastereomeric salt twice using MTBE30g, and 16.6g of diastereomeric salt was obtained. Subsequently, 18g of the sodium-hydroxide aqueous solutions was added 15%, the extraction using MTBE20g was performed twice after stirring for 30 minutes at 25 degrees C, after doubling an organic layer, the solvent was distilled off, and (R)-1-(3, 4-dimethoxy phenyl) ethylamine 8.8g (50.8%ee) was obtained.

[0036] The washings after washing the mother liquor and diastereomeric salt which were obtained above was doubled, it washed 5% using 50g of the sodium-hydroxide aqueous solutions, the solvent was distilled off, and (S)-1-(3, 4-dimethoxy phenyl) ethylamine 11.2g (62.4%ee) was obtained.

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TECHNICAL FIELD

[The technical field to which invention belongs] this invention relates to the optical-resolution technique of 1-phenyl ethylamines.

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PRIOR ART

[Description of the Prior Art] The optically active substance of 1-phenyl ethylamines is a compound useful as intermediate fields, such as the physic and a pesticide. The technique of carrying out optical resolution of the racemic modification in a solvent, using an optical-activity mandelic acid as technique of obtaining the optically active substance of such 1-phenyl ethylamines etc. is common, after melting racemic modification and the optical-activity mandelic acid of 1-phenyl ethylamines in a solvent especially, the diastereomeric salt of the optically active substance of 1-phenyl ethylamines and an optical-activity mandelic acid is obtained, and the technique of subsequently carrying out the alkali treatment of this diastereomeric salt etc. is learned widely.
[0003] Although the technique using water (JP,56-26848,A), aqueous ammonia (JP,6-1757,A), and a methanol (Bull.Chem.Soc.Jpn., 66, 3414 (1993)) as a solvent at the time of obtaining diastereomeric salt conventionally etc. is proposed The technique using water is difficult for the filterability of the obtained diastereomeric salt to filter it bad. The technique using aqueous ammonia needed the special facility for dealing with aqueous ammonia, and since the technique using a methanol had little yield of the optical-activity 1-phenyl ethylamines made into the purpose, it was not able to be said that each of such technique was the technique which may fully be satisfied industrially.

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EFFECT OF THE INVENTION

[Effect of the Invention] According to the technique of this invention, optical resolution of the 1-phenyl ethylamines can be easily carried out with high yield, without using a special facility.

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TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] Then, this invention person resulted in this invention, as a result of inquiring zealously that the technique of carrying out optical resolution of the 1-phenyl ethylamines with easy and high yield should be developed, without using a special facility.

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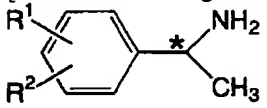
MEANS

[Means for Solving the Problem] That is, this invention is a general formula (1).



(1)

(R1 and R2 show a hydrogen atom, a halogen atom, an alkoxy group, a halo alkyl group, or a nitro group among a formula, respectively, and * shows an asymmetric carbon atom.) However, R1 R2 is not a chlorine atom simultaneously. An optical-activity mandelic acid is used for 1-phenyl ethylamines shown, and it is a general formula (2).
R3 -O-R4 (2
(-- R3 shows the alkyl group of carbon numbers 1-6 among a formula, and R4 shows the alkyl group of carbon numbers 4-6, respectively The optical-resolution technique of 1-phenyl ethylamines characterized by carrying out optical resolution in the dialkyl ether shown by) is offered.
[0006]
[Embodiments of the Invention] As a halogen atom [on 1-phenyl ethylamines applied to this invention, and in a substituent R1 and R2], a methoxy machine, the ethoxy base, etc. are illustrated as an alkoxy group, and a fluorine atom, a chlorine atom, a bromine atom, etc. are illustrated for a truffe ****** methyl group, difluoromethyl group, a ********** methyl group, etc. as a halo alkyl group, respectively.
[0007] As such 1-phenyl ethylamines For example, 1-phenyl ethylamine, 1-(2-fluoro phenyl) ethylamine, 1-(3-fluoro phenyl) ethylamine, 1-(2-chlorophenyl) ethylamine, 1-(3-chlorophenyl) ethylamine, 1-(2-****** phenyl) ethylamine, 1-(monochrome halo substitute phenyl) ethylamines, such as 1-(3-****** phenyl) ethylamine 1-(monochrome alkoxy substitute phenyl) ethylamines, such as 1-(2-methoxypheny) ethylamine and 1-(3-methoxypheny) ethylamine 1-(dialkoxy substitute phenyl) ethylamines, such as 1-(3, 4-dimethoxy phenyl) ethylamine 1-(2-truffe ****** methylphenyl) ethylamine, 1-(3-truffe ****** methylphenyl) ethylamine, 1-(nitroglycerine phenyl) ethylamines, such as 1-(halo alkylation phenyl) ethylamines, such as 1-(3-difluoro methylphenyl) ethylamine, 1-(2-nitroglycerine phenyl) ethylamine, and 1-(3-nitroglycerine phenyl) ethylamine, are mentioned. Each of these 1-phenyl ethylamines can be easily manufactured by the ********** (Leukert) reaction which uses acetophenones as a raw material [Organic Reaction Vol.5, pp.301-330 (1949)].
[0008] Although two kinds of optically active substance centering on the asymmetric carbon atom shown by * exists in 1-phenyl ethylamines shown by such general formula (1), 1-phenyl ethylamines used for the technique of this invention may be those mixture, and it may be racemic modification.
[0009] an optical-activity mandelic acid -- any of D-mandelic acid and L-mandelic acid -- you may be -- the amount used -- 1-phenyl ethylamines -- receiving -- usually -- 0.1-1.2 mol twice -- it is a twice as many 0.3-1 mol domain as this preferably
[0010] substituent R3 in the dialkyl ether shown by the general formula (2) ****** -- the alkyl group of the carbon numbers 1-6, such as a methyl group, an ethyl group, and n-propyl group, -- substituent R4 ****** -- the alkyl group of the carbon numbers 4-6, such as n-butyl, t-butyl, and n-hexyl machine, is mentioned, respectively As such dialkyl ether, a methyl-t-butyl ether, an ethyl-t-butyl ether, a methyl-n-butyl ether, an ethyl-n-butyl ether, etc. are mentioned, for example, and a methyl-t-butyl ether (MTBE is called hereafter.) is used preferably especially. These dialkyl ether mixes independent or two sorts or more, respectively, is used, and may contain the organic solvent and water of further others. The amount of such dialkyl ether used is usually a twice [2 - 100 weight] as many domain as this to 1-phenyl ethylamines.
[0011] What is necessary is to obtain the diastereomeric salt of the optically active substance of 1-phenyl ethylamines, and an optical-activity mandelic acid, and just to carry out the alkali treatment of this diastereomeric salt subsequently, after melting 1-phenyl ethylamines and an optical-activity mandelic acid in the dialkyl ether in case of optical resolution, for example.
[0012] It faces melting 1-phenyl ethylamines and an optical-activity mandelic acid in the dialkyl ether, 1-phenyl ethylamines and an optical-activity mandelic acid may be added, for example to the dialkyl ether, both may be melted, the dialkyl ether solution of 1-phenyl ethylamines and the dialkyl ether solution of an optical-activity mandelic acid may be mixed, and the salt with 1-phenyl ethylamines and the optical-activity mandelic acid which both were made to react and obtained them further beforehand may be melted in the dialkyl ether. A melting temperature is usually a domain below the boiling point of 15 degrees C or more and the dialkyl ether.
[0013] Although one [of 1-phenyl ethylamines] optically active substance forms the diastereomeric salt with an optical-activity mandelic acid preferentially and this diastereomeric salt separates by usual technique, for example, the technique of cooling and

condensing etc., you may make such diastereomeric salt separate by putting or stirring as it is by the case after lysis.
[0014] Although this is taken out after a precipitation of diastereomeric salt and it dissociates with a mother liquor, such diastereomeric salt is excellent in filterability, and can separate both easily by usual filtration operation etc.
[0015] The diastereomeric salt of the optically active substance of 1-phenyl ethylamines and the optical-activity mandelic acid which are obtained in this way is easily led to the optically active substance of 1-phenyl ethylamines by carrying out an alkali treatment.
[0016] In case of an alkali treatment, bases, such as a sodium hydroxide, a potassium hydroxide, a sodium carbonate, and a sodium hydrogencarbonate, are usually used, and the amount used is usually a twice as many 1-5 mol domain as this to diastereomeric salt. Such a base is usually used as aqueous solution, and the concentration is usually 5 - 20% of the weight of a domain preferably one to 50% of the weight.
[0017] The domain of processing temperature is usually -10-50 degrees C that what is necessary is just to mix the aqueous solution and diastereomeric salt of a base in case of an alkali treatment, for example.
[0018] Although the optically active substance of 1-phenyl ethylamines generates by such alkali treatment, this may be taken out by the technique of separating what carried out the layer separation in the reaction mixture after an alkali treatment by the case etc., and may be easily taken out from this reaction mixture by the technique of carrying out extraction processing, for example using an organic solvent insoluble in water, and carrying out solvent distilling off of the obtained organic layer etc. In the case of the latter, as an insoluble organic solvent, aromatic system solvents, such as ester system solvents, such as ether system solvents, such as the same dialkyl ether and the same diethylether, and a dioxane, and ethyl acetate, toluene, a xylene, and a chlorobenzene, etc. are used for water with having described above, for example, and the amount used is usually a twice [0.1 - 5 weight] as many domain as this to the diastereomeric salt used for the previous alkali treatment.
[0019] In addition, reaction mixture after taking out the optically active substance of 1-phenyl ethylamines contains an optical-activity mandelic acid, and such optical-activity mandelic acids can be easily collected from this reaction mixture, and it can carry out a reuse to the technique of this invention. Although it extracts in the same water using an insoluble organic solvent and the technique of carrying out solvent distilling off of the obtained organic layer etc. is mentioned to it with having described above after adding mineral acids, such as a hydrochloric acid, a sulfuric acid, and a phosphoric acid, for example to a water layer and making the pH into the domain of 0.5-2 as the recovery technique of such an optical-activity mandelic acid Since a reuse can be carried out to the technique of this invention, without distilling a solvent out of the obtained organic layer when the dialkyl ether is used as such an organic solvent, it is desirable.
[0020] Although the optically active substance of 1-phenyl ethylamines is obtained in this way, the optically active substance of another side which is an antipode with this is contained in the mother liquor after previous filtration operation separates diastereomeric salt, and after washing usual technique, for example, a mother liquor, from such a mother liquor using the alkaline aqueous solutions, such as the sodium-hydroxide aqueous solution, etc., it can be easily obtained by the technique of distilling off a solvent etc.

[Translation done.]

* NOTICES *

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1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

EXAMPLE

[Example] Hereafter, this invention is not limited by these examples although an example explains this invention to a detail more. In addition, it asked for the optical purity of obtained 1-phenyl ethylamines by the high-speed liquid chromatographic-analysis method for using an optical-activity column.

[0023] Example 1(RS)-1-phenyl-ethylamine 56g was melted in MTBE60g, it heated at 45 degrees C under stirring, and, in addition, the solution which, subsequently to MTBE180g, melted and obtained 31.7g of L-mandelic acids to this under stirring at this temperature was further stirred for 30 minutes at this temperature over 30 minutes. Then, cool to 20 degrees C over 6 hours, and the diastereomeric salt of a (S)-1-phenyl ethylamine and L-mandelic acid was made to separate, subsequently, by filtration operation, diastereomeric salt was obtained and the mother liquor was obtained simultaneously. After washing this diastereomeric salt twice using MTBE100g, it was made to dry, and 56.8g of diastereomeric salt was obtained. Subsequently, 185g of the sodium-hydroxide aqueous solutions was added 5%, the extraction using MTBE45g was performed twice after stirring for 30 minutes at 25 degrees C, after doubling an organic layer, the solvent was distilled off, and (S)-1-phenyl-ethylamine 25.2g (87%ee) was obtained.

[0024] After having doubled the washings after washing the mother liquor and diastereomeric salt which were obtained above and adding 18g of the sodium-hydroxide aqueous solutions 5%, extraction processing using MTBE30g was performed twice, after doubling an organic layer, the solvent was distilled off, and (R)-1-phenyl-ethylamine 30.8g (70.4%ee) was obtained.

[0025] Example 2(RS)-1-(2-fluoro phenyl) ethylamine 5g is melted in MTBE10g. The solution which melted and obtained 2.46g of L-mandelic acids to MTBE30g is dropped and added to this over 30 minutes, stirring under this temperature, after heating at 45 degrees C, the bottom of stirring of this, and. Furthermore, after stirring for 30 minutes, cool to 20 degrees C over 3 hours, and the diastereomeric salt of a (S)-1-(2-fluoro phenyl) ethylamine and L-mandelic acid was made to separate, subsequently, by filtration operation, diastereomeric salt was obtained and the mother liquor was obtained simultaneously. It dried, after washing this diastereomeric salt twice using MTBE10g, and 4.6g of diastereomeric salt was obtained. Subsequently, 16g of the sodium-hydroxide aqueous solutions was added 5%, the extraction using MTBE10g was performed twice after stirring for 30 minutes at 25 degrees C, after doubling an organic layer, the solvent was distilled off, and (S)-1-(2-fluoro phenyl) ethylamine 2.2g (87.2%ee) was obtained.

[0026] The washings after washing the mother liquor and diastereomeric salt which were obtained above was doubled, after washing 5% using 13g of the sodium-hydroxide aqueous solutions, the solvent was distilled off, and (R)-1-(2-fluoro phenyl) ethylamine 2.8g (71.6%ee) was obtained.

[0027] Example 3(RS)-1-(3-methoxypheny) ethylamine 5g is melted in MTBE20g. The solution which melted and obtained 2g of L-mandelic acids to MTBE20g is dropped and added to this over 30 minutes, stirring under this temperature, after heating at 50 degrees C, the bottom of stirring of this, and. Furthermore, after stirring for 30 minutes, cool to 20 degrees C over 3 hours, and the diastereomeric salt of a (S)-1-(3-methoxypheny) ethylamine and L-mandelic acid was made to separate, subsequently, by filtration operation, diastereomeric salt was obtained and the mother liquor was obtained simultaneously. It dried, after washing this diastereomeric salt twice using MTBE10g, and 4.1g of diastereomeric salt was obtained. Subsequently, 16g of the sodium-hydroxide aqueous solutions was added 5%, the extraction using MTBE10g was performed twice after stirring for 30 minutes at 25 degrees C, after doubling an organic layer, the solvent was distilled off, and (S)-1-(3-methoxypheny) ethylamine 2g (55.4%ee) was obtained.

[0028] After washing 5% using 13g of the sodium-hydroxide aqueous solutions together with a washings after washing the mother liquor and diastereomeric salt which were obtained above, the solvent was distilled off, and (R)-1-(3-methoxypheny) ethylamine 3g (43.8%ee) was obtained.

[0029] The solution which mixed and obtained example of comparison 1(RS)-1-(3-methoxypheny) ethylamine 5g, 2g [of L-mandelic acids], and methanol 13g was heated at 60 degrees C, and was stirred for 30 minutes under this temperature. When it became 30 degrees C, cooling to 20 degrees C over 3 hours, 0.01g of the diastereomeric salt of a (S)-1-(3-methoxypheny) ethylamine (99.9% of the optical-purity (S) fields, 0.1% of (R) fields) and L-mandelic acid was added as seed crystal. After cooling at 20 degrees C, by filtration operation, the diastereomeric salt of a (S)-1-(3-methoxypheny) ethylamine and L-mandelic acid was obtained, and the mother liquor was obtained simultaneously. It dried, after washing this diastereomeric salt once using methanol 3g, and 1.2g of diastereomeric salt was obtained. Subsequently, 10g of the sodium-hydroxide aqueous solutions was added 5%, the extraction using toluene 10g was performed twice after stirring for 30 minutes at 25 degrees C, after doubling an organic layer, the solvent was distilled off, and (S)-1-(3-methoxypheny) ethylamine 0.6g (88.2%ee) was obtained.

[0030] After having doubled the washings after washing the mother liquor and diastereomeric salt which were obtained above

and adding toluene 10g, it washed 5% using 13g of the sodium-hydroxide aqueous solutions, the solvent was distilled off, and (R)-1-(3-methoxypheny) ethylamine 4.4g (12.2%ee) was obtained.
[0031] Example 4(RS)-1-(2-nitroglycerine phenyl) ethylamine 3.1g is melted in MTBE15g. The solution which melted and obtained 1.3g of L-mandelic acids to MTBE15g is dropped and added to this over 30 minutes, stirring under this temperature, after heating at 45 degrees C, the bottom of stirring of this, and. Furthermore, after stirring for 30 minutes, cool to 20 degrees C over 3 hours, and the diastereomeric salt of a (S)-1-(2-nitroglycerine phenyl) ethylamine and L-mandelic acid was made to separate, subsequently, by filtration operation, diastereomeric salt was obtained and the mother liquor was obtained simultaneously. It dried, after washing this diastereomeric salt twice using MTBE5g, and 2.4g of diastereomeric salt was obtained. Subsequently, 10g of the sodium-hydroxide aqueous solutions was added 5%, the extraction using MTBE10g was performed twice after stirring for 30 minutes at 25 degrees C, after doubling an organic layer, the solvent was distilled off, and (S)-1-(2-nitroglycerine phenyl) ethylamine 1.3g (90.4%ee) was obtained.
[0032] The washings after washing the mother liquor and diastereomeric salt which were obtained above was doubled, after washing 5% using 10g of the sodium-hydroxide aqueous solutions, the solvent was distilled off, and (R)-1-(2-nitroglycerine phenyl) ethylamine 1.8g (61.6%ee) was obtained.
[0033] Example 5(RS)-1-(3-truffe ****** methylphenyl) ethylamine 4g is melted in MTBE20g. The solution which melted and obtained 1.6g of L-mandelic acids to MTBE15g is dropped and added to this over 30 minutes, stirring under this temperature, after heating at 45 degrees C, the bottom of stirring of this, and. Furthermore, after stirring for 30 minutes, cool to 20 degrees C over 3 hours, and the diastereomeric salt of a (S)-1-(3-truffe ****** methylphenyl) ethylamine and L-mandelic acid was made to separate, subsequently, by filtration operation, diastereomeric salt was obtained and the mother liquor was obtained simultaneously. It dried, after washing this diastereomeric salt twice using MTBE5g, and 3.3g of diastereomeric salt was obtained. Subsequently, 10g of the sodium-hydroxide aqueous solutions was added 5%, the extraction using MTBE10g was performed twice after stirring for 30 minutes at 25 degrees C, after doubling an organic layer, the solvent was distilled off, and (S)-1-(3-truffe ****** methylphenyl) ethylamine 1.8g (60%ee) was obtained.
[0034] The washings after washing the mother liquor and diastereomeric salt which were obtained above was doubled, it washed 5% using 10g of the sodium-hydroxide aqueous solutions, the solvent was distilled off, and (R)-1-(3-truffe ****** methylphenyl) ethylamine 2.2g (50%ee) was obtained.
[0035] Example 6(RS)-1-(3, 4-dimethoxy phenyl) ethylamine 20g is melted in MTBE30g. The solution which melted and obtained 7.6g of L-mandelic acids to MTBE80g is dropped and added to this over 30 minutes, stirring under this temperature, after heating at 45 degrees C, the bottom of stirring of this, and. Furthermore, after stirring for 30 minutes, cool to 20 degrees C over 3 hours, and the diastereomeric salt of a (R)-1-(3, 4-dimethoxy phenyl) ethylamine and L-mandelic acid was made to separate, subsequently, by filtration operation, diastereomeric salt was obtained and the mother liquor was obtained simultaneously. It dried, after washing this diastereomeric salt twice using MTBE30g, and 16.6g of diastereomeric salt was obtained. Subsequently, 18g of the sodium-hydroxide aqueous solutions was added 15%, the extraction using MTBE20g was performed twice after stirring for 30 minutes at 25 degrees C, after doubling an organic layer, the solvent was distilled off, and (R)-1-(3, 4-dimethoxy phenyl) ethylamine 8.8g (50.8%ee) was obtained.
[0036] The washings after washing the mother liquor and diastereomeric salt which were obtained above was doubled, it washed 5% using 50g of the sodium-hydroxide aqueous solutions, the solvent was distilled off, and (S)-1-(3, 4-dimethoxy phenyl) ethylamine 11.2g (62.4%ee) was obtained.

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(19)日本国特許庁（ＪＰ）　(12)公開特許公報（Ａ）　(11)特許出願公開番号

特開平9－278718

(43)公開日　平成９年(1997)10月28日

(51)Int.Cl.⁶	識別記号	庁内整理番号	ＦＩ	技術表示箇所
Ｃ０７Ｃ 211/27		8828－4H	Ｃ０７Ｃ 211/27	
209/88		8828－4H	209/88	
211/29		8828－4H	211/29	
213/10		7457－4H	213/10	
217/58		7457－4H	217/58	

審査請求　未請求　請求項の数５　ＯＬ　（全　５　頁）　最終頁に続く

(21)出願番号　特願平8－84041

(22)出願日　平成８年(1996)４月５日

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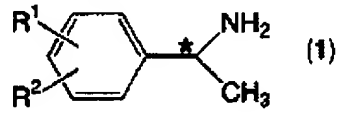
(54)【発明の名称】　１－フェニルエチルアミン類の光学分割方法

(57)【要約】　（修正有）

【課題】　特別の設備を用いることなく容易かつ高収量で１－フェニルエチルアミン類を光学分割する方法を提供する。

【解決手段】　一般式１



(1)

（R¹，Ｒ²は水素、ハロゲン、アルコキシ基、ハロアルキル基またはニトロ基．＊は不斉炭素を示し．ただしＲ¹とＲ²とが同時に塩素ではない。）の１－フェニルエチルアミン類を光学活性マンデル酸を用いて一般式（２）

Ｒ³－Ｏ－Ｒ⁴　（２）

（Ｒ³はＣ１～６のアルキル基、Ｒ⁴はＣ４～６のアルキル基を示す。）のジアルキルエーテル中で光学分割する１－フェニルエチルアミン類の光学分割方法。

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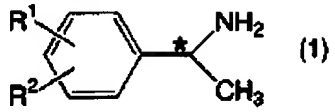
【特許請求の範囲】

【請求項１】一般式（１）



（式中、R¹．R²はそれぞれ水素原子、ハロゲン原子、アルコキシ基、ハロアルキル基またはニトロ基を示し．＊は不斉炭素原子を示す。ただし．R¹とR²とが同時に塩素原子であることはない。）で示される１－フェニルエチルアミン類を光学活性マンデル酸を用いて一般式（２）

R’－O－R’　　（２）

（式中、R’は炭素数１～６のアルキル基を、R’は炭素数４～６のアルキル基をそれぞれ示す。）で示されるジアルキルエーテル中で光学分割することを特徴とする１－フェニルエチルアミン類の光学分割方法。

【請求項２】一般式（１）で示される１－フェニルエチルアミン類および光学活性マンデル酸を一般式（２）で示されるジアルキルエーテルに溶解したのち、１－フェニルエチルアミン類の光学活性体と光学活性マンデル酸とのジアステレオマー塩を得、次いで該ジアステレオマー塩をアルカリ処理することを特徴とする１－フェニルエチルアミン類の光学分割方法。

【請求項３】ジアルキルエーテルがメチル－ｔ－ブチルエーテルであることを特徴とする請求項１または請求項２に記載の１－フェニルエチルアミン類の光学分割方法。

【請求項４】ジアルキルエーテルの使用量が、１－フェニルエチルアミン類に対して２～１００重量倍であることを特徴とする請求項１または請求項２に記載の１－フェニルエチルアミン類の光学分割方法。

【請求項５】光学活性マンデル酸の使用量が、１－フェニルエチルアミン類に対して０．１～１．２モル倍であることを特徴とする請求項１または請求項２に記載の１－フェニルエチルアミン類の光学分割方法。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】本発明は．１－フェニルエチルアミン類の光学分割方法に関する。

【０００２】

【従来の技術】１－フェニルエチルアミン類の光学活性体は医薬、農薬などの中間体として有用な化合物である。かかる１－フェニルエチルアミン類の光学活性体を得る方法としては、そのラセミ体を光学活性マンデル酸を用いて溶媒中で光学分割する方法などが一般的であり．中でも１－フェニルエチルアミン類のラセミ体と光学活性マンデル酸とを溶媒に溶解したのち、１－フェニルエチルアミン類の光学活性体と光学活性マンデル酸とのジアステレオマー塩を得．次いで該ジアステレオマー

2

塩をアルカリ処理する方法などが広く知られている。

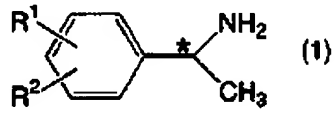
【０００３】従来よりジアステレオマー塩を得る際の溶媒として水（特開昭５６－２６８４８号公報）．アンモニア水（特開平６－１７５７号公報）．メタノール（Bull.Chem.Soc.Jpn.,66,3414(1993)）を用いる方法などが提案されているが、水を用いる方法は得られたジアステレオマー塩の濾過性が悪くそれを濾過することが困難であり．アンモニア水を用いる方法はアンモニア水を取り扱うための特別の設備を必要とし、メタノールを用いる方法は目的とする光学活性１－フェニルエチルアミン類の収量が少ないため、これらの方法はいずれも工業的に十分に満足し得る方法であるとは言えなかった。

【０００４】

【発明が解決しようとする課題】そこで本発明者は、特別の設備を用いることなく．容易にかつ高い収量で１－フェニルエチルアミン類を光学分割する方法を開発するべく鋭意検討した結果、本発明に至った。

【０００５】

【課題を解決するための手段】すなわち本発明は．一般式（１）



（式中、R¹．R²はそれぞれ水素原子、ハロゲン原子、アルコキシ基、ハロアルキル基またはニトロ基を示し．＊は不斉炭素原子を示す。ただし．R¹とR²とが同時に塩素原子であることはない。）で示される１－フェニルエチルアミン類を光学活性マンデル酸を用いて一般式（２）

R’－O－R’　　（２）

（式中、R’は炭素数１～６のアルキル基を、R’は炭素数４～６のアルキル基をそれぞれ示す。）で示されるジアルキルエーテル中で光学分割することを特徴とする１－フェニルエチルアミン類の光学分割方法を提供するものである。

【０００６】

【発明の実施の形態】本発明に適用される１－フェニルエチルアミン類において．置換基R¹．R²におけるハロゲン原子としてはフッ素原子、塩素原子、臭素原子などが．アルコキシ基としてはメトキシ基、エトキシ基などが．ハロアルキル基としてはトリフルオロメチル基、ジフルオロメチル基、トリクロロメチル基などがそれぞれ例示される。

【０００７】かかる１－フェニルエチルアミン類としては．例えば１－フェニルエチルアミン．１－（２－フルオロフェニル）エチルアミン、１－（３－フルオロフェニル）エチルアミン、１－（２－クロロフェニル）エチルアミン、１－（３－クロロフェニル）エチルアミン、１－（２－ブロモフェニル）エチルアミン、１－（３－

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Operator: SetColorSpace

Position: 152

http://www6.ipdl.jpo.go.jp/tj[redacted]enttrns...=&N0349=&N0704=1E_N/;%3f6=878%3e7///////

ブロモフェニル）エチルアミンなどの1－（モノハロ置換フェニル）エチルアミン類、1－（2－メトキシフェニル）エチルアミン、1－（3－メトキシフェニル）エチルアミンなどの1－（モノアルコキシ置換フェニル）エチルアミン類．1－（3，4－ジメトキシフェニル）エチルアミンなどの1－（ジアルコキシ置換フェニル）エチルアミン類．1－（2－トリフルオロメチルフェニル）エチルアミン、1－（3－トリフルオロメチルフェニル）エチルアミン、1－（3－ジフルオロメチルフェニル）エチルアミンなどの1－（ハロアルキル置換フェニル）エチルアミン類、1－（2－ニトロフェニル）エチルアミン、1－（3－ニトロフェニル）エチルアミンなどの1－（ニトロフェニル）エチルアミン類などが挙げられる。これらの1－フェニルエチルアミン類はいずれもアセトフェノン類を原料とするロイカルト（Ｌｅｕｋｅｒｔ）反応によって容易に製造することができる〔Organic Reaction Vol.5,pp.301-330(1949)〕。

【０００８】かかる一般式（1）で示される1－フェニルエチルアミン類には＊で示される不斉炭素原子を中心とする2種類の光学活性体が存在するが、本発明の方法に用いられる1－フェニルエチルアミン類はそれらの混合物であってもよいし、ラセミ体であってもよい。

【０００９】光学活性マンデル酸はD－マンデル酸、L－マンデル酸のいずれであってもよく．その使用量は、1－フェニルエチルアミン類に対して通常は0．1～1．2モル倍．好ましくは0．3～1モル倍の範囲である。

【００１０】一般式（2）で示されるジアルキルエーテルにおける置換基R'としてはメチル基、エチル基、n－プロピル基などの炭素数1～6のアルキル基が．置換基R'としてはn－ブチル基、t－ブチル基、n－ヘキシル基などの炭素数4～6のアルキル基がそれぞれ挙げられる。かかるジアルキルエーテルとしては、例えばメチル－t－ブチルエーテル．エチル－t－ブチルエーテル．メチル－n－ブチルエーテル、エチル－n－ブチルエーテルなどが挙げられ．中でもメチル－t－ブチルエーテル（以下．ＭＴＢＥと称する。）が好ましく用いられる。これらのジアルキルエーテルはそれぞれ単独または2種以上を混合して用いられ、さらには他の有機溶媒や水を含有していてもよい。かかるジアルキルエーテルの使用量は1－フェニルエチルアミン類に対して通常2～１００重量倍の範囲である。

【００１１】光学分割に際しては、例えば1－フェニルエチルアミン類および光学活性マンデル酸をジアルキルエーテルに溶解させたのち．1－フェニルエチルアミン類の光学活性体と光学活性マンデル酸とのジアステレオマー塩を得．次いで該ジアステレオマー塩をアルカリ処理すればよい。

【００１２】1－フェニルエチルアミン類および光学活性マンデル酸をジアルキルエーテルに溶解させるに際しては．例えばジアルキルエーテルに1－フェニルエチルアミン類と光学活性マンデル酸とを加えて両者を溶解してもよいし、1－フェニルエチルアミン類のジアルキルエーテル溶液と光学活性マンデル酸のジアルキルエーテル溶液とを混合してもよく．さらには予め両者を反応させて得た1－フェニルエチルアミン類と光学活性マンデル酸との塩をジアルキルエーテルに溶解してもよい。溶解温度は通常１５℃以上．ジアルキルエーテルの沸点以下の範囲である。

【００１３】溶解後、通常の方法、例えば冷却．濃縮する方法などによって、1－フェニルエチルアミン類の一方の光学活性体が優先的に光学活性マンデル酸とのジアステレオマー塩を形成し．該ジアステレオマー塩が析出するが、場合によってはそのまま静置または撹拌することによってかかるジアステレオマー塩を析出させてもよい。

【００１４】ジアステレオマー塩の析出後、これを取り出し．母液と分離するが．かかるジアステレオマー塩は濾過性に優れており、通常の濾過操作などによって容易に両者を分離することができる。

【００１５】かくして得られる1－フェニルエチルアミン類の光学活性体と光学活性マンデル酸とのジアステレオマー塩は、アルカリ処理されることによって容易に1－フェニルエチルアミン類の光学活性体へ導かれる。

【００１６】アルカリ処理に際して通常は水酸化ナトリウム．水酸化カリウム、炭酸ナトリウム、炭酸水素ナトリウムなどの塩基が用いられ、その使用量は通常ジアステレオマー塩に対して1～5モル倍の範囲である。かかる塩基は通常．水溶液として用いられ．その濃度は通常1～５０重量%．好ましくは5～２０重量%の範囲である。

【００１７】アルカリ処理に際しては．例えば塩基の水溶液およびジアステレオマー塩を混合すればよく．処理温度は通常－１０～５０℃の範囲である。

【００１８】かかるアルカリ処理によって1－フェニルエチルアミン類の光学活性体が生成するが、これは、場合によってはアルカリ処理後の反応混合物において層分離したものを分液する方法などによって取り出してもよいし．該反応混合物から．例えば水に不溶の有機溶媒を用いて抽出処理し、得られた有機層を溶媒留去する方法などによって容易に取り出してもよい。後者の場合、水に不溶の有機溶媒としては．例えば前記したと同様のジアルキルエーテルやジエチルエーテル．ジオキサンなどのエーテル系溶媒、酢酸エチルなどのエステル系溶媒、トルエン、キシレン、クロロベンゼンなどの芳香族系溶媒などが用いられ、その使用量は先のアルカリ処理に用いたジアステレオマー塩に対して通常0．1～5重量倍の範囲である。

【００１９】なお、1－フェニルエチルアミン類の光学活性体を取り出した後の反応混合物は光学活性マンデル

PCL XL error

Subsystem: KERNEL

Error: IllegalOperatorSequence

Operator: SetColorSpace

Position: 154

http://www6.ipdl.jpo.go.jp/ti[illegible]enttrns...=&N0349=&N0704=1E_N/;%3f6=878%3e7///////

酸を含有するものであり．かかる光学活性マンデル酸は該反応混合物から容易に回収し、本発明の方法に再使用することができる。かかる光学活性マンデル酸の回収方法としては、例えば水層に塩酸、硫酸．リン酸などの鉱酸を加えてそのｐＨを０．５～２の範囲としたのち、前記したと同様の水に不溶の有機溶媒を用いて抽出し、得られた有機層を溶媒留去する方法などが挙げられるが、かかる有機溶媒としてジアルキルエーテルを用いた場合には．得られた有機層から溶媒を留去することなく本発明の方法に再使用し得るため、好ましい。

【００２０】かくして１－フェニルエチルアミン類の光学活性体が得られるが、これとの対掌体である他方の光学活性体は、先の濾過操作によってジアステレオマー塩を分離した後の母液に含まれており．かかる母液から通常の方法、例えば母液を水酸化ナトリウム水溶液などのアルカリ性水溶液などを用いて洗浄したのち溶媒を留去する方法などによって容易に得ることができる。

【００２１】

【発明の効果】本発明の方法によれば．特別の設備を用いることなく．容易にかつ高収量で１－フェニルエチルアミン類を光学分割することができる。

【００２２】

【実施例】以下．実施例によって本発明をより詳細に説明するが、本発明はこれら実施例により限定されるものではない。なお．得られた１－フェニルエチルアミン類の光学純度は．光学活性カラムを用いる高速液体クロマトグラフ分析法によって求めた。

【００２３】実施例１

（ＲＳ）－１－フェニルエチルアミン５６ｇをＭＴＢＥ６０ｇに溶解し．撹拌下．４５℃に加熱し、次いで同温度で撹拌下、これにＬ－マンデル酸３１．７ｇをＭＴＢＥ１８０ｇに溶解して得た溶液を３０分かけて加え、さらに同温度で３０分間撹拌した。その後、６時間かけて２０℃まで冷却して、（Ｓ）－１－フェニルエチルアミンとＬ－マンデル酸とのジアステレオマー塩を析出させ．次いで濾過操作によって、ジアステレオマー塩を得．同時に母液を得た。このジアステレオマー塩を、ＭＴＢＥ１００ｇを用いて２回洗浄したのち乾燥させて、ジアステレオマー塩５６．８ｇを得た。次いで．５％水酸化ナトリウム水溶液１８５ｇを加えて２５℃で３０分間撹拌後、ＭＴＢＥ４５ｇを用いる抽出を２回行い、有機層を合わせたのち溶媒を留去して．（Ｓ）－１－フェニルエチルアミン２５．２ｇ（８７％ｅｅ）を得た。

【００２４】上記で得た母液とジアステレオマー塩を洗浄したのちの洗液とを合わせ、５％水酸化ナトリウム水溶液１８ｇを加えたのち．ＭＴＢＥ３０ｇを用いる抽出処理を２回行い．有機層を合わせたのち溶媒を留去して．（Ｒ）－１－フェニルエチルアミン３０．８ｇ（７０．４％ｅｅ）を得た。

【００２５】実施例２

（ＲＳ）－１－（２－フルオロフェニル）エチルアミン５ｇをＭＴＢＥ１０ｇに溶解し、これを撹拌下．４５℃に加熱したのち．同温度下で撹拌しながらこれにＬ－マンデル酸２．４６ｇをＭＴＢＥ３０ｇに溶解して得た溶液を３０分かけて滴下して加え、さらに３０分間撹拌したのち、３時間かけて２０℃まで冷却して、（Ｓ）－１－（２－フルオロフェニル）エチルアミンとＬ－マンデル酸とのジアステレオマー塩を析出させ、次いで濾過操作によって、ジアステレオマー塩を得．同時に母液を得た。このジアステレオマー塩を、ＭＴＢＥ１０ｇを用いて２回洗浄したのち乾燥して、ジアステレオマー塩４．６ｇを得た。次いで、５％水酸化ナトリウム水溶液１６ｇを加えて２５℃で３０分間撹拌後．ＭＴＢＥ１０ｇを用いる抽出を２回行い、有機層を合わせたのち溶媒を留去して、（Ｓ）－１－（２－フルオロフェニル）エチルアミン２．２ｇ（８７．２％ｅｅ）を得た。

【００２６】上記で得た母液とジアステレオマー塩を洗浄したのちの洗液とを合わせ、５％水酸化ナトリウム水溶液１３ｇを用いて洗浄したのち溶媒を留去して．（Ｒ）－１－（２－フルオロフェニル）エチルアミン２．８ｇ（７１．６％ｅｅ）を得た。

【００２７】実施例３

（ＲＳ）－１－（３－メトキシフェニル）エチルアミン５ｇをＭＴＢＥ２０ｇに溶解し、これを撹拌下．５０℃に加熱したのち．同温度下で撹拌しながらこれにＬ－マンデル酸２ｇをＭＴＢＥ２０ｇに溶解して得た溶液を３０分かけて滴下して加え．さらに３０分間撹拌したのち．３時間かけて２０℃まで冷却して．（Ｓ）－１－（３－メトキシフェニル）エチルアミンとＬ－マンデル酸とのジアステレオマー塩を析出させ．次いで濾過操作によって、ジアステレオマー塩を得．同時に母液を得た。このジアステレオマー塩を、ＭＴＢＥ１０ｇを用いて２回洗浄したのち乾燥して、ジアステレオマー塩４．１ｇを得た。次いで、５％水酸化ナトリウム水溶液１６ｇを加えて２５℃で３０分間撹拌後．ＭＴＢＥ１０ｇを用いる抽出を２回行い、有機層を合わせたのち溶媒を留去して、（Ｓ）－１－（３－メトキシフェニル）エチルアミン２ｇ（５５．４％ｅｅ）を得た。

【００２８】上記で得た母液とジアステレオマー塩を洗浄したのちの洗液と合わせ．５％水酸化ナトリウム水溶液１３ｇを用いて洗浄したのち溶媒を留去して．（Ｒ）－１－（３－メトキシフェニル）エチルアミン３ｇ（４３．８％ｅｅ）を得た。

【００２９】比較例１

（ＲＳ）－１－（３－メトキシフェニル）エチルアミン５ｇ．Ｌ－マンデル酸２ｇおよびメタノール１３ｇを混合して得た溶液を６０℃に加熱し、同温度下、３０分間撹拌した。３時間かけて２０℃まで冷却しながら．３０℃になった時点で種晶として（Ｓ）－１－（３－メトキシフェニル）エチルアミン（光学純度（Ｓ）体９９．９

PCL XL error

Subsystem: KERNEL

Error: IllegalOperatorSequence

Operator: SetColorSpace

Position: 154

http://www6.ipdl.jpo.go.jp/tenttrns...=&N0349=&N0704=1E_N/;%3f6=878%3e7///////

%．（R）体0．1%）とL－マンデル酸とのジアステレオマー塩0．01gを加えた。20℃に冷却後．濾過操作によって（S）－1－（3－メトキシフェニル）エチルアミンとL－マンデル酸とのジアステレオマー塩を得．同時に母液を得た。このジアステレオマー塩を、メタノール3gを用いて1回洗浄したのち乾燥して．ジアステレオマー塩1．2gを得た。次いで、5%水酸化ナトリウム水溶液10gを加えて25℃で30分間撹拌後．トルエン10gを用いる抽出を2回行い、有機層を合わせたのち溶媒を留去して、（S）－1－（3－メトキシフェニル）エチルアミン0．6g（88．2%ee）を得た。

【0030】上記で得た母液とジアステレオマー塩を洗浄したのちの洗液とを合わせ、トルエン10gを加えたのち．5%水酸化ナトリウム水溶液13gを用いて洗浄し．溶媒を留去して、（R）－1－（3－メトキシフェニル）エチルアミン4．4g（12．2%ee）を得た。

【0031】実施例4

（RS）－1－（2－ニトロフェニル）エチルアミン3．1gをMTBE15gに溶解し．これを撹拌下、45℃に加熱したのち、同温度下で撹拌しながらこれにL－マンデル酸1．3gをMTBE15gに溶解して得た溶液を30分かけて滴下して加え、さらに30分間撹拌したのち、3時間かけて20℃まで冷却して、（S）－1－（2－ニトロフェニル）エチルアミンとL－マンデル酸とのジアステレオマー塩を析出させ、次いで濾過操作によって、ジアステレオマー塩を得．同時に母液を得た。このジアステレオマー塩を、MTBE5gを用いて2回洗浄したのち乾燥して．ジアステレオマー塩2．4gを得た。次いで、5%水酸化ナトリウム水溶液10gを加えて25℃で30分間撹拌後、MTBE10gを用いる抽出を2回行い、有機層を合わせたのち溶媒を留去して．（S）－1－（2－ニトロフェニル）エチルアミン1．3g（90．4%ee）を得た。

【0032】上記で得た母液とジアステレオマー塩を洗浄したのちの洗液とを合わせ、5%水酸化ナトリウム水溶液10gを用い洗浄したのち溶媒を留去して．（R）－1－（2－ニトロフェニル）エチルアミン1．8g（61．6%ee）を得た。

【0033】実施例5

（RS）－1－（3－トリフルオロメチルフェニル）エチルアミン4gをMTBE20gに溶解し、これを撹拌＊下．45℃に加熱したのち．同温度下で撹拌しながらこれにL－マンデル酸1．6gをMTBE15gに溶解して得た溶液を30分かけて滴下して加え、さらに30分間撹拌したのち．3時間かけて20℃まで冷却して、（S）－1－（3－トリフルオロメチルフェニル）エチルアミンとL－マンデル酸とのジアステレオマー塩を析出させ、次いで濾過操作によって、ジアステレオマー塩を得．同時に母液を得た。このジアステレオマー塩を、MTBE5gを用いて2回洗浄したのち乾燥して．ジアステレオマー塩3．3gを得た。次いで、5%水酸化ナトリウム水溶液10gを加えて25℃で30分間撹拌後．MTBE10gを用いる抽出を2回行い、有機層を合わせたのち溶媒を留去して、（S）－1－（3－トリフルオロメチルフェニル）エチルアミン1．8g（60%ee）を得た。

【0034】上記で得た母液とジアステレオマー塩を洗浄したのちの洗液とを合わせ、5%水酸化ナトリウム水溶液10gを用いて洗浄し．溶媒を留去して、（R）－1－（3－トリフルオロメチルフェニル）エチルアミン2．2g（50%ee）を得た。

【0035】実施例6

（RS）－1－（3，4－ジメトキシフェニル）エチルアミン20gをMTBE30gに溶解し、これを撹拌下．45℃に加熱したのち．同温度下で撹拌しながらこれにL－マンデル酸7．6gをMTBE80gに溶解して得た溶液を30分かけて滴下して加え、さらに30分間撹拌したのち．3時間かけて20℃まで冷却して、（R）－1－（3，4－ジメトキシフェニル）エチルアミンとL－マンデル酸とのジアステレオマー塩を析出させ．次いで濾過操作によって、ジアステレオマー塩を得．同時に母液を得た。このジアステレオマー塩を、MTBE30gを用いて2回洗浄したのち乾燥して．ジアステレオマー塩16．6gを得た。次いで、15%水酸化ナトリウム水溶液18gを加えて25℃で30分間撹拌後．MTBE20gを用いる抽出を2回行い．有機層を合わせたのち溶媒を留去して、（R）－1－（3，4－ジメトキシフェニル）エチルアミン8．8g（50．8%ee）を得た。

【0036】上記で得た母液とジアステレオマー塩を洗浄したのちの洗液とを合わせ、5%水酸化ナトリウム水溶液50gを用いて洗浄し．溶媒を留去して、（S）－1－（3，4－ジメトキシフェニル）エチルアミン11．2g（62．4%ee）を得た。

フロントページの続き

(51)Int.Cl.*	識別記号	庁内整理番号	FI		技術表示箇所
// C07B 57/00	360	7419－4H	C07B 57/00	360	
C07M 7:00					

PCL XL error

Subsystem: KERNEL

Error: IllegalOperatorSequence

Operator: SetColorSpace

Position: 152